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Percutaneous tulobuterol preparation and process for producing the same

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(54)Title: PERCUTANEOUS TULOBUTEROL PREPARATION AND PROCESS FOR PRODUCING THE SAME

(54)発明の名称 経皮吸収型ツロブテロール製剤とその製造法

(57) Abstract

A percutaneous tulobuterol preparation obtained by laminating a pressure-sensitive adhesive layer comprising as the main component a synthetic rubber containing micro-crystalline tulobuterol of 2 to 20 μm in average particle size onto a support; in particular, a percutaneous tulobuterol preparation wherein the micro-crystalline tulobuterol is one obtained by dissolving tulobuterol and a pressure-sensitive adhesive comprising as the main component a synthetic resin in a good solvent followed by recrystallization; and a process for producing the preparation which comprises homogeneously dissolving the adhesive and tulobuterol in a good solvent, applying the resulting adhesive solution onto one face of a peelable film and drying to thereby form an adhesive layer; then laminating the adhesive layer onto a support; and recrystallizing tulobuterol at 10 to 30 °C to thereby give an adhesive layer wherein microcrystals of 2 to 20 μm in average particle size have been homogeneously dispersed. The preparation is excellent in the long-lasting drug effect. The above process makes it possible to efficiently produce the preparation.

（５７）要約

本発明は、平均粒径２～２０μｍの微細結晶状のツロブテロールを含有する合成ゴムを主成分とする粘着剤層と支持体とを積層してなる経皮吸収型ツロブテロール製剤、特に微細結晶状のツロブテロールが、ツロブテロールと合成ゴムを主成分とする粘着剤とを良溶媒中に溶解後、再結晶させて得られるものである経皮吸収型ツロブテロール製剤に関する。また本発明は、該粘着剤とツロブテロールとを良溶媒中で均一に溶解した後、この粘着剤溶液を剥離性フィルムの一方面に塗布乾燥して粘着剤層を形成後、粘着剤層を支持体に貼り合わせ、１０～３０℃で再結晶させて平均粒径２～２０μｍの範囲の微細結晶が均一に分散されてなる粘着剤層を形成する経皮吸収型ツロブテロール製剤の製造法に関する。

本発明の経皮吸収型ツロブテロール製剤はツロブテロールの薬効持続性に優れている。本発明の製造方法においては、上記の製剤が効率よく製造される。

Abstract of the Disclosure

The present invention relates to a percutaneous absorption type tulobuterol preparation comprising a support and an adhesive layer mainly composed of a synthetic rubber comprising microcrystalline tulobuterol having an average particle size of 2-20 μm laminated thereon, particularly, a percutaneous absorption type tulobuterol preparation obtained by dissolving tulobuterol and an adhesive mainly composed of a synthetic rubber in a good solvent and subjecting the resulting solution to recrystallization. In addition, the present invention relates to a process for producing a percutaneous absorption type tulobuterol preparation, comprising homogeneously dissolving an adhesive mainly composed of a synthetic rubber and tulobuterol in a good solvent, applying the resulting adhesive solution on one surface of a release film and drying same to form an adhesive layer, transferring the adhesive layer to a support, and recrystallization at 10-30℃ to form an adhesive layer comprising microcrystalline tulobuterol having an average particle size of 2-20 μm uniformly dispersed therein. The percutaneous absorption type tulobuterol preparation of the present invention is superior in duration of the drug effect of tulobuterol. The production process of the present invention enables efficient production of the above preparation.

SPECIFICATION

PERCUTANEOUS ABSORPTION TYPE TULOBUTEROL PREPARATION AND PRODUCTION PROCESS THEREOF

Technical Field

The present invention relates to a percutaneous absorption type tulobuterol preparation for a sustained and continuous administration of tulobuterol through the skin into the body upon application thereof to the skin surface, and a production process thereof. More particularly, the present invention relates to a percutaneous absorption type tulobuterol preparation capable of sustaining an effective concentration of tulobuterol in blood for an extended time period upon application thereof to the skin surface, and to an efficient production process thereof.

Background Art

Tulobuterol selectively acts on $\beta 2$ receptor of the sympathetic nerve and relaxes the bronchial smooth muscle. Thus, it has been widely used for treating chronic bronchitis, bronchial asthma and the like in an attempt to reduce respiratory distress of patients with respiratory tract stricture. The tulobuterol is generally administered into the body by oral administration using, for example, tablets, dry syrup and the like or by inhalation administration using, for example, aerosol. These methods, however, are associated with the problems of difficulty in administering to infants and the like, emergence of side-effects such as palpitation and tremor caused by steep increase in blood concentration of the drug, short duration of drug effect, and the like.

To solve these problems, the present applicant has already proposed a plaster containing tulobuterol (see Japanese Patent Unexamined Publication No. 4-99720 and others). When used in the form of a plaster, the drug is percutaneously administered, which makes administration to infants and the like easy and ensures quick absorption thereof through the skin. In addition, the duration of drug effect can be prolonged and the side-effects can be reduced.

A plaster containing tulobuterol provides the above-mentioned advantages. However, a need exists for a more prolonged duration of drug effect.

Disclosure of the Invention

For a sustained percutaneous absorption of tulobuterol, the tulobuterol in an adhesive should not be entirely dissolved, but preferably remains in a crystalline form. Nevertheless, the relationship between the crystal particle size of tulobuterol and the duration of drug effect has not been sufficiently clarified yet.

The present inventors have taken note of this aspect and conducted intensive studies to find that there exists an optimal range in the relation between the particle size of recrystallized tulobuterol and the duration of drug effect thereof, which resulted in the completion of the present invention.

Accordingly, the present invention provides the following.

(1) A percutaneous absorption type tulobuterol preparation comprising a support and an adhesive layer mainly composed of a synthetic rubber which contains microcrystalline tulobuterol having an average particle size of 2-20 μm.

(2) The percutaneous absorption type tulobuterol preparation of (1) above, wherein the microcrystalline tulobuterol having an average particle size of 2-20 μm can be obtained by dissolving tulobuterol and an adhesive mainly composed of a synthetic rubber in a good solvent and subjecting the resulting solution to recrystallization.

(3) The percutaneous absorption type tulobuterol preparation of (2) above, wherein the recrystallization is carried out at a temperature of 10-30℃.

(4) The percutaneous absorption type tulobuterol preparation of any one of (1) to (3) above, wherein the microcrystalline tulobuterol has an average particle size of 5-20 μm.

(5) A process for producing a percutaneous absorption type tulobuterol preparation, comprising homogeneously dissolving an adhesive mainly composed of a synthetic rubber and tulobuterol in a good solvent, applying this adhesive solution on one surface of a release film, drying same to give an adhesive layer, transferring the adhesive layer to a support, and recrystallizing tulobuterol at 10-30℃ to form an adhesive layer containing microcrystalline tulobuterol having an average

particle size of 2-20 μ m uniformly dispersed therein.

(6) The process for producing a percutaneous absorption type tulobuterol preparation according to (5) above, wherein the average particle size of the microcrystalline tulobuterol is 5-20 μ m.

Brief Description of the Drawings

Fig. 1 is a graph showing the results of Experimental Example 1.

Fig. 2 is a graph showing the results of Experimental Example 2.

Detailed Description of the Invention

In the present invention, the adhesive layer mainly comprises an adhesive containing a synthetic rubber as the main component and tulobuterol. For adjustment of adhesive force, a low molecular weight polymer, a thermoplastic resin and the like may be contained.

The synthetic rubber to be used in the present invention may be polyisobutylene, polyisoprene, styrene-butadiene block copolymer, styrene-butadiene-styrene block copolymer (SBS), styrene-isoprene-styrene block copolymer (SIS) and mixtures thereof.

The low molecular weight polymer to be added for adjusting adhesive force may be polybutene, acrylic adhesive, ethylene/vinyl acetate copolymer (EVA) and the like. A thermoplastic resin added to an adhesive mainly composed of a synthetic rubber acts as an appropriate diffusion obstacle when tulobuterol diffuses and moves within the adhesive. This in turn achieves sustained and efficient release of tulobuterol to the skin surface to enable long term percutaneous absorption thereof by the body, thus ultimately prolonging the duration of drug effect. In consequence, the maintenance of an effective blood concentration, namely, superior duration of the drug effect, can be achieved, thereby reducing the frequency of administration (the number of applications of plaster per unit time), which in turn secures reduced irritation to the skin. Such thermoplastic resin is, for example, in a crystalline state at ordinary temperature and has a softening point of 50-250℃, preferably 50-150℃. Specific examples thereof include natural resins such as rosin and derivatives thereof, terpene resin, terpene · phenol resin and the like, and synthetic resins such as petroleum resin, alkyl · phenol resin, xylene resin and the like. One or more kinds of these resins may be added in a proportion of not more than 50% by weight, preferably 5-40% by weight, of the synthetic rubber component.

In the present invention, it is not desirable, unlike the conventional

plasters, to add a mineral oil as a carrier for dissolution or release of the drug to an adhesive layer. This is because the interaction between the drug and the mineral oil or impurities in the mineral oil may degrade the stability of the drug contained in the preparation with the passage of time. When a mineral oil, which is a liquid, is used as a carrier of a drug, the release of the drug from the adhesive may possibly become extremely fast to produce problems that the side-effects may be caused by a sudden increase in blood concentration or long duration of the drug effect, which is an advantageous aspect of a plaster, may be lost.

The thickness of the adhesive layer is desirably 20-100 μ m, preferably 20-50 μ m, so that it can stand a long time adhesion to the skin surface.

In the present invention, the tulobuterol to be contained in the above-mentioned adhesive layer is a medicine to exhibit a pharmacological effect. It is partly dissolved in the adhesive layer and partly exits as crystals. The concentration of the tulobuterol dissolved in the adhesive layer directly affects the rate of percutaneous absorption and decreases by being absorbed through the skin. Inasmuch as an excess tulobuterol beyond the saturation solubility in the adhesive to be used is dispersed in the adhesive as crystals, the amount of tulobuterol that can be contained in the adhesive is adequately determined according to the adhesive to be used. On the other hand, crystalline tulobuterol dissolves while a plaster is being applied, and tulobuterol thus dissolved is absorbed through the skin, thereby supplementarily supplying tulobuterol to the adhesive, that has been dissolved and decreased by the absorption through the skin. As a result, high levels of percutaneous absorption of tulobuterol can be sustained for a long time, thereby maintaining effective blood concentration for an extended period of time.

In this way, the present invention can accomplish superior duration of drug effect due to the use of microcrystalline tulobuterol having a specific average particle size.

In the present invention, the crystalline tulobuterol include microcrystals having an average particle size of 2-20 μ m, preferably 5-20 μ m.

Those having a particle size of less than 2 μ m have greater total surface areas than do those having a greater particle size when they are contained in a preparation in the same amount. The greater surface area increases the

dissolution rate of the drug in the adhesive layer to increase drug release in the early stages and may cause side-effects due to the accompanying steep increase in blood concentration, thus failing to sufficiently sustain the drug effect.

When the particle size exceeds 20 μ m, the effect is generally considered to be reverse of the effect of the particles having the size of less than 2 μ m. In this case again, a greater particle size leads to an exposure of a multitude of crystals on the surface of an adhesive layer to be in contact with the skin. In consequence, the exposed drug particles do not disperse in the adhesive but are dissolved in water present at the application site and directly released on the skin surface to cause an increased drug release in the early stages. This may lead to side-effects due to the accompanying steep increase in blood concentration or insufficient duration of the drug effect.

In the present invention, the shape of the microcrystals varies depending on the kind of adhesive, tulobuterol content and the like, and may be particle, sphere, square, plate, flake, column, rod, needle, fiber and the like. The crystals are preferably in uniform dispersion rather than in aggregation.

The particle size of the microcrystals in the present invention is measured in a Feret diameter determined using a microscope . The Feret diameter is conventionally known and described in, for example, Handbook of Powder engineering (compiled by Society of Powder engineering), pp. 1-2, Nikkan Kogyo Shinbunsha, 1986.

The microcrystalline tulobuterol in the present invention are produced by dissolving an adhesive mainly composed of a synthetic rubber and tulobuterol in a good solvent and then subjecting the resulting solution to recrystallization.

More specifically, the present invention involves the following steps. That is, the above-mentioned adhesive and tulobuterol are homogeneously dissolved in one or more good solvents to give an adhesive solution and this solution is used to form a membrane. As a result, the drug contained in more than a saturation solubility in the above-mentioned adhesive is precipitated as crystals in the above-mentioned adhesive. The microcrystals thus produced by recrystallization have almost the same size and can be re-dissolved.

Preferable good solvent includes non-polar solvents such as hexane,

toluene, cyclohexane and heptane.

The recrystallization temperature is generally 10-30℃, preferably 20-30℃. When it is less than 10℃, the crystal particles have a size of less than 2 μm, whereas when it exceeds 30℃, they exceed 20 μm in size.

In the present invention, a support on which an adhesive layer is to be laminated is subject to no particular limitation as long as it can form, on one surface thereof, an adhesive layer containing tulobuterol and support same, and it has a skin conformability. In general, one substantially non-impermeable to tulobuterol, particularly one having a flexibility that allows the support to follow curves and movement of the skin to the extent that remarkable discomfort is not caused when it is adhered to the skin surface, is preferably used. Examples thereof include plastic films of polyethylene, polypropylene, polyester, poly(vinyl acetate), ethylene/vinyl acetate copolymer, poly(vinyl chloride), polyurethane and the like, metal foils of aluminum, tin and the like, a single layer film made of a nonwoven fabric, cloth, paper and the like, or a laminate film thereof. Such support has a thickness of generally 5-500 μm, preferably 5-200 μm. The surface of the support where an adhesive layer is to be laminated is preferably subjected to corona discharge treatment, plasma treatment, oxidizing treatment for an improved adhesion to an adhesive layer and anchor effect.

The preparation of the present invention is, for example, obtained by the following process. An adhesive comprising a synthetic rubber as the main component and tulobuterol are homogeneously dissolved in a good solvent, this adhesive solution is applied on one surface of a release film and dried to give an adhesive layer. The adhesive layer is laminated on a support, and subjected to recrystallization at 10-30℃, so that microcrystalline tulobuterol having an average particle size 2-20 μm may be uniformly dispersed in the adhesive layer. In this way, the preparation of the present invention can be produced.

The release film is exemplified by paper and plastic films. The release film is preferably rendered removable by coating with a silicone resin, fluorocarbon resin and the like.

The percutaneous absorption type tulobuterol preparation of the present invention is administered by the application to the skin. The administration is usually performed by the application of a preparation containing tulobuterol in an amount of 0.5-2 mg/sheet, once a day.

Examples

In the following Examples and Comparative Examples, "part" means "part by weight".

Example 1

High molecular weight polyisobutylene (28.5 parts, viscosity average molecular weight 990000, VISTANEX MML-80, manufactured by Exxon Chemical), low molecular weight polyisobutylene (43 parts, viscosity average molecular weight 60000, HIMOL 6H, manufactured by NIPPON PETROCHEMICALS CO., LTD.), polybutene (8.5 parts, viscosity average molecular weight 1260, HV-300, manufactured by NIPPON PETROCHEMICALS CO., LTD.) and alicyclic petroleum resin (20 parts, softening point 100℃, Arkon P-100, manufactured by ARAKAWA CHEMICAL INDUSTRIES LTD.) were dissolved in hexane to give a polyisobutylene adhesive solution (solid content 25%). Tulobuterol was added thereto to make the tulobuterol content in an adhesive layer (in plaster layer) 10%, admixed and thoroughly stirred. Then, it was coated on a release film (release liner) so that the thickness after drying became 20 μ m and dried to form an adhesive layer. Then, the adhesive layer was transferred to a polyester film side of a laminate film as a support which was made of a polyester film (thickness 6 μ m) and a polyester nonwoven fabric (20 g/m^2), and allowed to age for 7 days at 25℃ to give a percutaneous absorption type preparation of the present invention. In the obtained percutaneous absorption type preparation, tulobuterol crystals having an average particle size of about 10 μ m were uniformly dispersed in the adhesive layer.

Comparative Example 1

In the same manner as in Example 1 except that the aging was carried out at 5℃ for 7 days, a percutaneous absorption type preparation was obtained. In the obtained percutaneous absorption type preparation, crystalline tulobuterol having an average particle size of about 1 μ m were uniformly dispersed in the adhesive layer.

Comparative Example 2

In the same manner as in Example 1 except that the aging was carried out at 40℃ for 7 days, a percutaneous absorption type preparation was obtained. In the obtained percutaneous absorption type preparation, crystalline tulobuterol having an average particle size of about 30 μ m were

uniformly dispersed in the adhesive layer.

Example 2

A styrene-isoprene-styrene block copolymer (33.3 parts, Cariflex TR1107, manufactured by Shell Chemicals), polybutene (HV-300, 25 parts) and alicyclic petroleum resin (41.7 parts, softening point 100℃, Arkon P-100) were dissolved in toluene to give a solution (solid content 25%). Tulobuterol was added thereto to make the tulobuterol content in an adhesive layer (in plaster layer) 10%, admixed and thoroughly stirred. Then, it was coated on a release film (release liner) so that the thickness after drying became 20 μ m and dried to form an adhesive layer. Then, the adhesive layer was transferred to a polyester film side of a laminate film as a support which was made of a polyester film (thickness 6 μ m) and a polyester nonwoven fabric (20 g/m^2), and aged for 7 days at 10℃ to give a percutaneous absorption type preparation of the present invention. In the obtained percutaneous absorption type preparation, crystalline tulobuterol having an average particle size of about 5 μ m were uniformly dispersed in the adhesive layer.

Example 3

A styrene-butadiene block copolymer (50 parts, Solprene 411, manufactured by Asahi Chemical Industry Co., Ltd.) and alicyclic petroleum resin (50 parts, softening point 105℃, ESCOREZ 5300, manufactured by Exxon Chemical) were dissolved in toluene to give a solution having a solid content of 25%. Tulobuterol was added thereto to make the tulobuterol content in an adhesive layer (in plaster layer) 20%, admixed and thoroughly stirred. Then, it was coated on a release film (release liner) so that the thickness after drying became 40 μ m and dried to form an adhesive layer. Then, the adhesive layer was transferred to a polyester film (thickness 12 μ m) as a support, and aged for 7 days at 30℃ to give a percutaneous absorption type preparation of the present invention. In the obtained percutaneous absorption type preparation, crystalline tulobuterol having an average particle size of about 15 μ m were uniformly dispersed in the adhesive layer.

Example 4

Isoprene rubber (60 parts, Kuraprene IR-10, manufactured by KURARAY CO., LTD.) and hydrogenated rosin derivative resin (40 parts, softening point 97℃, Pentalyn H, manufactured by HERCULES INCORPORATED) were dissolved in toluene to give a solution having a solid

content of 25%. Tulobuterol was added thereto to make the tulobuterol content in an adhesive layer (in plaster layer) 10%, admixed and thoroughly stirred. Then, it was coated on a release film (release liner) so that the thickness after drying became 20 μm and dried to form an adhesive layer. Then, the adhesive layer was transferred to a polyester film (thickness 12 μm) as a support, and aged for 7 days at 25℃ to give a percutaneous absorption type preparation of the present invention. In the obtained percutaneous absorption type preparation, crystalline tulobuterol having an average particle size of about 10 μm were uniformly dispersed in the adhesive layer. The aging for 7 days leveled the amount of the precipitated crystalline tulobuterol, whereby the release of tulobuterol from said preparation can be almost stabilized.

Example 5

In the same manner as in Example 1 except that the aging was carried out at 30℃ for 7 days, a percutaneous absorption type preparation was obtained. In the obtained percutaneous absorption type preparation, crystalline tulobuterol having an average particle size of about 20 μm were uniformly dispersed in the adhesive layer.

Experimental Example 1

(Test Method)

Drug releasability from a preparation was examined according to Japan Pharmacopoeia, General Test, Dissolution Test Method 2, with respect to the percutaneous absorption type preparations obtained in Examples and Comparative Examples. Operation conditions were as follows.

Dissolution tester : (NTR-VS6, TOYAMA SANGYO CO., LTD.)
Sample size : 10 cm^2
Distilled water : 32℃, 500 ml
Rotation of puddle : 50 r.p.m.
Determination of absorbance : 211 nm (SHIMADZU CORPORATION UV-160A)

(Test Results)

The test results are shown in Fig. 1. A preparation containing tulobuterol having a particle size of less than 2 μm (Comparative Example 1) and a preparation containing tulobuterol having a particle size of more than 20 μm (Comparative Example 2) showed high releasability from the early

stage, giving concern about possible side-effects caused by the steep increase of blood concentration upon actual application.

Experimental Example 2

(Test Method)

The percutaneous absorption type preparations obtained in Example 1 and Comparative Example 1 were applied to the pre-shaved dorsal region of rabbits, and the blood concentration profiles of tulobuterol after application were examined. The details of the test method were as follows.

Sample size : 50 cm^2

Application site : pre-shaved dorsal region of rabbits

Application time : 24 hours

Blood concentration determination method : gas chromatography (HP-5890)

(Test Results)

The test results are shown in Fig. 2.

The preparation which showed high releasability from the early stage in Experimental Example 1 (Comparative Example 1) also showed steep increase of blood concentration in rabbit in the early stages. In contrast, the preparation of the present invention (Example 1) showed sustained fine blood concentration profiles.

Effects of the Invention

The preparation of the present invention is superior in the duration of the drug effect of tulobuterol, since, as the tulobuterol dissolved in the adhesive layer is percutaneously absorbed and decreases, the microcrystalline tulobuterol obtained by recrystallization is successively re-dissolved in the adhesive layer and percutaneously absorbed. In consequence, the frequency of application of the preparation can be reduced and irritation to the skin can be lessened.

In addition, the production process of the present invention enables efficient production of the above-mentioned preparation.

In the claims which follow and in the preceding description of the invention, except where the context requires otherwise due to express language or necessary implication, the word "comprising" is used in the sense of "including", that is the features specified may be associated with further features in various embodiments of the invention.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. A percutaneous absorption type tulobuterol preparation comprising a support and an adhesive layer laminated thereon, the adhesive layer comprising a synthetic rubber and microcrystalline tulobuterol having an average particle size of 2-20μm.

2. The percutaneous absorption type tulobuterol preparation of claim 1, wherein the microcrystalline tulobuterol having an average particle size of 2-20μm is obtained by dissolving tulobuterol and an adhesive comprising a synthetic rubber in a solvent capable of dissolving tulobuterol and said adhesive, and subjecting the resulting solution to recrystallization.

3. The percutaneous absorption type tulobuterol preparation of claim 2, wherein the recrystallization is carried out at a temperature of 10-30°C.

4. The percutaneous absorption type tulobuterol preparation of any one of claims 1 to 3, wherein the microcrystalline tulobuterol has an average particle size of 5-20μm.

5. A process for producing a percutaneous absorption type tulobuterol preparation comprising the steps of:

(1) homogeneously dissolving an adhesive comprising a synthetic rubber and tulobuterol in a solvent capable of dissolving tolubuterol and said adhesive,

(2) applying the resulting adhesive solution on one surface of a release film and drying same to form an adhesive layer,

(3) transferring the adhesive layer to a support, and

(4) recrystallization at 10-30°C to form an adhesive layer comprising microcrystalline tulobuterol having an average particle size of 2-20μm uniformly dispersed therein.

6. The process of producing a percutaneous

absorption type tulobuterol preparation according to claim 5, wherein the microcrystalline tulobuterol has an average particle size of 5-20μm.

7. A percutaneous absorption type tulobuterol preparation substantially as herein described with reference to Example 1, Example 2, Example 3, Example 4 or Example 5.

8. A process for producing a percutaneous absorption type tulobuterol preparation substantially as herein described with reference to Example 1, Example 2, Example 3, Example 4 or Example 5.

Dated this 17th day of May 1999
Nitto Denko Corporation and Hokuriku Seryaku Co. Ltd.
By their Patent Attorneys
GRIFFITH HACK

FIG. 1

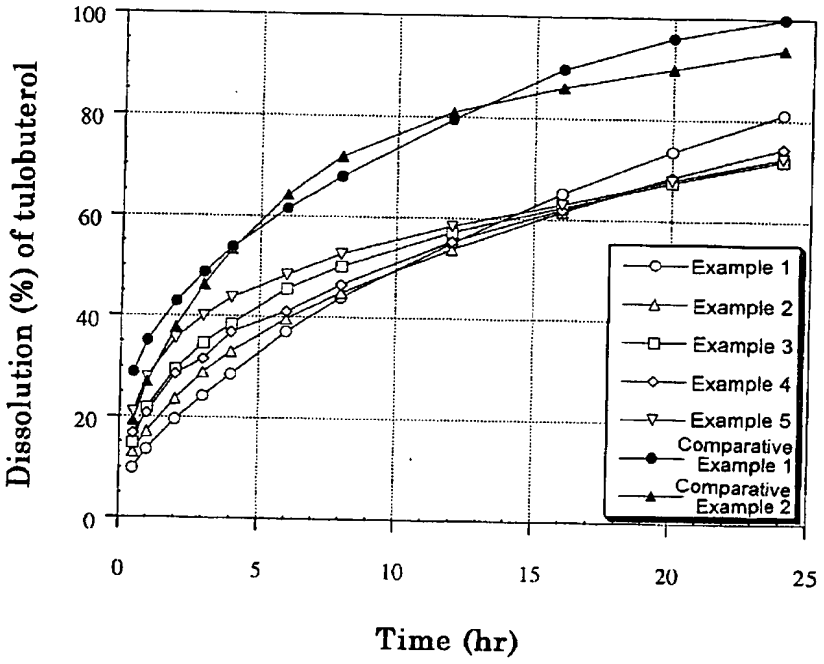
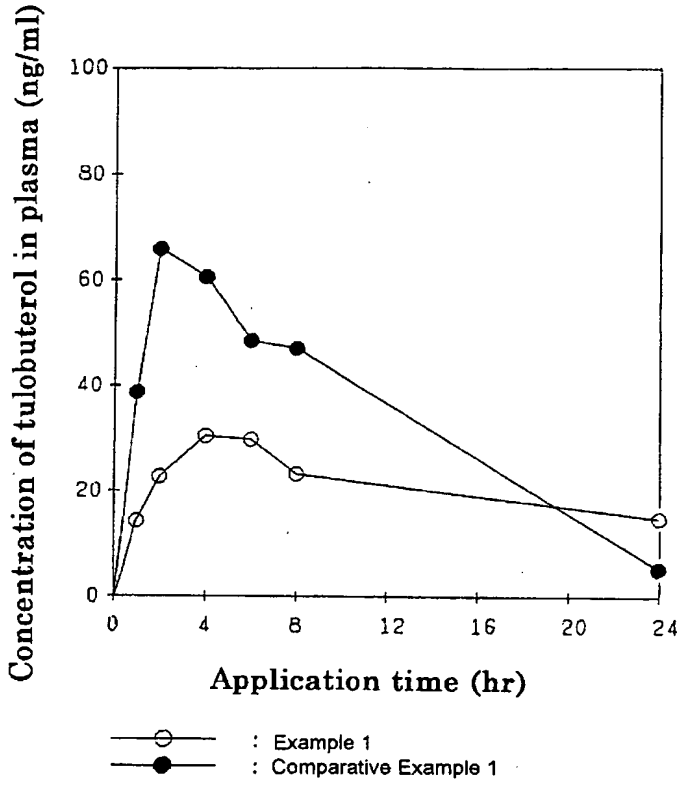

Dissolution (%) of tulobuterol
100
80
60
40
20
0
0
5
10
15
20
25
Time (hr)
Example 1
Example 2
Example 3
Example 4
Example 5
Comparative Example 1
Comparative Example 2

FIG. 2


Concentration of tulobuterol in plasma (ng/ml)
100
80
60
40
20
0
0
4
8
12
16
20
24
Application time (hr)
: Example 1
: Comparative Example 1